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CLINICAL IMPLICATIONS OF BASIC RESEARCH

Elizabeth G. Phimister, Ph.D., *Editor***Defining Metastatic Cell Latency**

Jeffrey W. Pollard, Ph.D.

Metastatic disease accounts for more than 90% of cancer deaths. For example, the life expectancy of women who have breast cancer has dramatically improved over the past 10 years, but women with metastatic disease have a 5-year survival rate of only 20%. Approximately 30% of women without evidence of metastatic disease at the time of resection of the primary tumor have metastatic disease develop later. Some women with small tumors and no evidence of lymph-node involvement have a recurrence 10 to 15 years after surgery. These and other observations suggest that cells from primary tumors can seed distant sites early and that these cells can lie dormant for many years until they “reawaken,” whereupon they develop into metastatic and usually lethal tumors. Since metastatic disease is a key component of tumor-related morbidity and mortality, it is essential to develop new therapeutics directed at these latent metastatic cells or at micrometastases before they develop into difficult-to-treat large tumors.

Pathological analyses suggest that tumor cells can seed to and be maintained in many different organs. How do they escape immune attack and survive? How is their dormant state maintained, and what stimulates their escape from dormancy? A study reported by Malladi et al.¹ begins to answer these questions. The investigators derived, from a human metastatic lung-cancer cell line and a breast-cancer cell line, latency-competent cells that seed distant sites after experimental tail-vein inoculation into immunocompromised mice but that remain largely dormant for several months. These cells form tumors when injected into orthotopic sites but do not grow in the metastatic context. Isolation of these latency-competent cells from the lung indicated that they had properties of stem cells: they had robust

expression of the transcription factors Sox9 and Sox2 (as do stem cells of mammary and lung adenocarcinomas, respectively) (Fig. 1). The authors also found that latency-competent cells entered a slowly proliferating state that is regulated by these Sox transcription factors. Despite the ability of these cells to survive for long periods at the sites of simulated metastasis, initial survival was very low, which suggested attrition by either mechanical or metabolic stress or through immune ablation.

Previous studies have shown that natural killer cells kill metastasizing cells, and Malladi et al. found that ablation of natural killer cells dramatically increased the ability of latency-competent cells to survive and metastasize. The level of natural killer cell activity is determined by the extent to which “inhibitory” and “activating” receptors are stimulated by their ligands; Malladi et al. observed that latency-competent cells expressed high levels of the inhibitory ligands, and this elevated level of expression protected these cells against ex vivo natural killer cell killing assays. Gene profiling also revealed that certain signaling pathways were altered in latency-competent cells, including down-regulation of Wnt signaling and high expression of the Wnt inhibitor, Dkk1. Knockdown of Dkk1 stimulated the proliferation of latency-competent cells and, through up-regulation of activating ligands, increased their susceptibility to killing by natural killer cells. They found a dramatically increased rate of metastatic tumor growth in mice that were depleted of natural killer cells, which suggested that a dip in or a waning of immunity is a contributory factor to the emergence of micrometastases from the latent state.

A major rate-limiting step for metastatic cells is at the stage of extravasation from the blood-

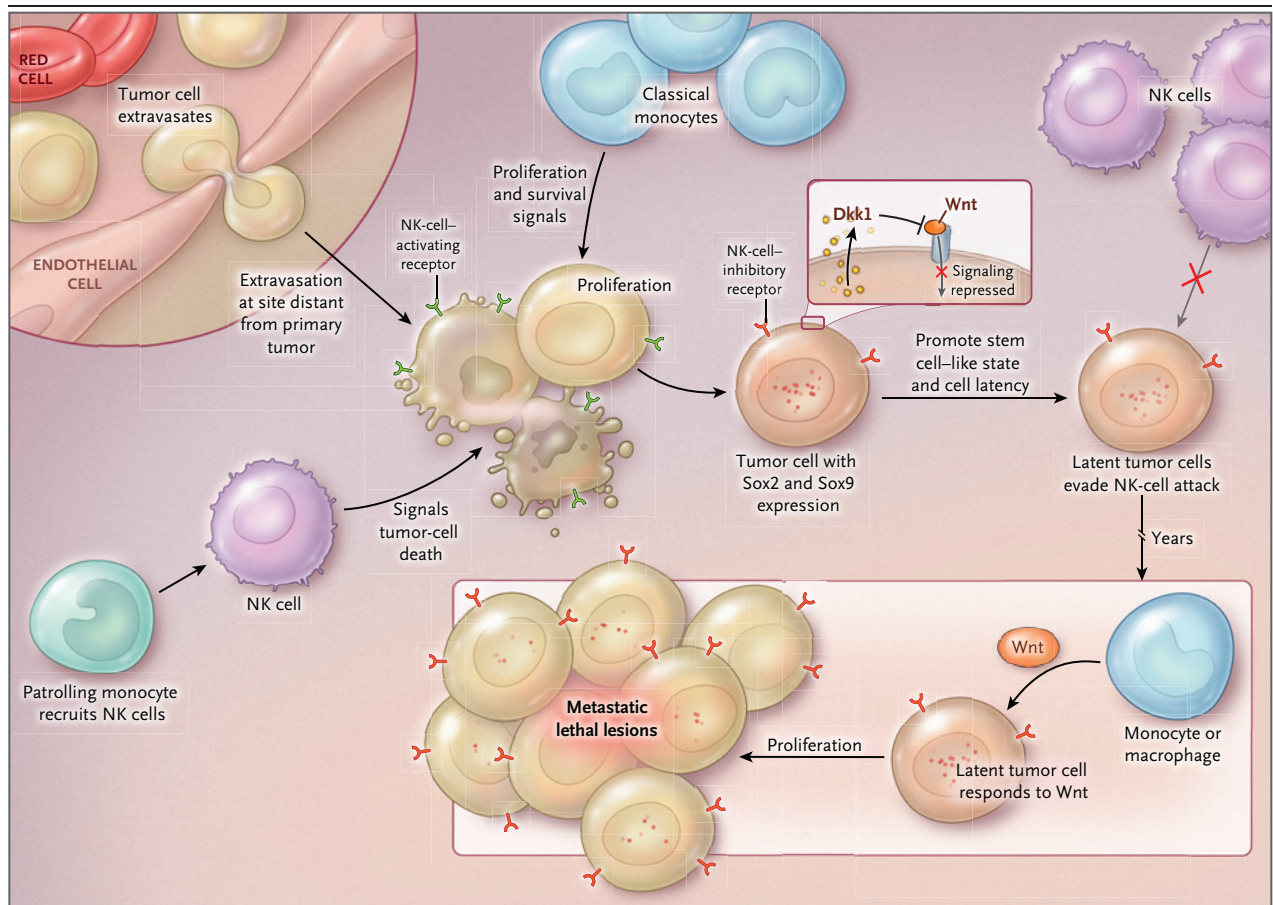


Figure 1. When the Tumor Cell Sleeps No More.

Metastatic tumor cells escape from the circulation to become established at distant sites. Patrolling monocytes recruit natural killer (NK) cells to these extravasating cells, which kill them, thus reducing seeding efficiency. Countering this effect are the classical monocytes, which are recruited to promote extravasation and survival of the cancer cells. A study recently reported by Malladi et al.¹ showed that rare surviving cells can enter into a latent stem-cell-like state characterized by Sox2 or Sox9 expression and that these cells evade NK cells through Dkk1-mediated inhibition of Wnt signaling that down-regulates NK-cell-activating receptors. They proposed that the cells undergo cycles of proliferation and death until a secondary event allows them to respond to Wnt proteins — perhaps expressed by monocytes or macrophages — that may increase expression of NK-cell-inhibitory ligands, whereupon they grow into metastatic lethal lesions.

stream into the target tissue (site of metastasis). Experimentally, natural killer cells represent a barrier to this process and are recruited by a subpopulation of patrolling nonclassical monocytes to the extravasating tumor cells.² The classical monocytes are also recruited to the site of invading tumor cells; these monocytes enhance tumor-cell extravasation and survival.³ The current study suggests that latency-competent cells survive because of the Dkk1-mediated dialing down of immunogenicity and Sox-maintained “stemness”: both of these states are known to

confer on the cell resistance to attack by natural killer cells. Latency-competent cells appear to stochastically undergo cycles of proliferation and loss, perhaps reflecting changing balances between the protumor and antitumor actions of the immune system.⁴ The results of the study by Malladi et al. need to be extended to less artificial models of metastatic latency, involving progressive heterogeneous spontaneously arising tumors in immune-competent mice. Nevertheless, their study points to the possibility that the eradication of latent metastatic cells might one

day be achieved therapeutically, perhaps by enhancing Wnt signaling in micrometastases (one means of achieving this would be through blocking of DKK1 binding) and coincident transfer of activated tumor-targeted natural killer cells.⁵ The danger of this approach is that Wnt ligands are protumoral and involved in metastasis. An alternative approach may be to find means of activating in the latency-competent cell expression of ligands that activate natural killer cells, making the latency-competent cells susceptible to attack.

Disclosure forms provided by the author are available at NEJM.org.

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